A Systematic Review of Cost-Effectiveness Research of Stroke Evaluation and Treatment

Robert G. Holloway, MD, MPH; Curtis G. Benesch, MD; Catherine R. Rahilly, BA; Caryn E. Courtright, BS

Background and Purpose—This work was undertaken to review research addressing the cost-effectiveness of stroke-related diagnostic, preventive, or therapeutic interventions.

Methods—We performed searches of MEDLINE, Excerpta Medica online, HealthSTAR, and Sciences Citation Index Expanded and examined the reference lists of the studies and reviews obtained. From these, we selected studies that reported an incremental analysis of cost per effect, in which the effect measure was life-years or quality-adjusted life-years. We abstracted data from each study using a standardized reporting form. Twenty-six articles met the eligibility criteria and were included in the review.

Results—The methodological quality of the articles reviewed has improved compared with previously reported. Many stroke evaluation and treatment policies may result in benefits to health that are considered worth their cost. Some interventions were considered cost-ineffective (anticoagulation in low-risk nonvalvular atrial fibrillation and surveillance with duplex ultrasound after endarterectomy). Different studies addressing the cost-effectiveness of screening asymptomatic carotid stenosis resulted in strikingly divergent conclusions, from being cost-effective to being detrimental. Other studies omitted important costs that, if included, would likely have had profound impact on their cost-effectiveness estimates.

Conclusions—Given the divergent conclusions drawn from studies addressing similar questions, it may be premature to use the results of cost-effectiveness research in developing stroke policy and practice guidelines. Successful implementation of such evaluations in the care of patients with stroke will depend on further standardization of methodology and critical appraisal of reported findings. (Stroke. 1999;30:1340-1349.)

Key Words: costs and cost analysis ■ cost-benefit analysis ■ stroke management

In the past decade, there have been extraordinary medical advances in the treatments available to stroke patients. Randomized controlled trials have demonstrated benefit for various interventions, including carotid endarterectomy for symptomatic1 and asymptomatic carotid stenosis,2 anticoagulation for nonvalvular atrial fibrillation (NVAF),3 tissue plasminogen activator (tPA) for acute stroke,4 and ticlopidine for transient cerebral ischemia or minor stroke.5 In addition, advances in imaging technology have provided sensitive, noninvasive techniques, such as magnetic resonance angiography (MRA) and transesophageal echocardiography (TEE), to aid in the evaluation of stroke patients.

Similar gains have been witnessed in elucidating of the economic impact of stroke. The cost of stroke has been studied in many countries, including the United States,6 Canada,7 Sweden,8 Scotland,9 Austria,10 New Zealand,11 the United Kingdom,12 Denmark,13 and the Netherlands.14 These studies verify the huge economic impact of stroke because stroke-related costs comprise 3% to 4% of the annual healthcare budget in some countries.9,10 In the United States, it has been estimated that the lifetime cost per person of first stroke in 1990 was $103 576.6

Although studies such as those cited above provide important information about the cost of stroke to society, they do not provide information about which treatments are the most efficient in reducing overall disease burden in the setting of economic constraints. Given the growing demands on scarce health resources and the large economic burden associated with stroke, defining the relative value of different stroke interventions is crucial. By simultaneously assessing the health effects and costs of different health interventions, cost-effectiveness analysis provides a research methodology to make such comparisons.15 Specifically, the objectives of cost-effectiveness analysis are to show the relative value of alternative interventions and to determine how efficiently these interventions improve health in target populations.

This study reviews research addressing the cost-effectiveness of stroke-related diagnostic, preventive, or therapeutic interventions. The objectives of this study were (1) to systematically obtain and review all published cost-effectiveness analyses of...
stroke evaluation and treatment and (2) to compare the relative value of those stroke interventions studied.

Subjects and Methods

Criteria for Considering Studies for Review

Studies were included if they performed a comparative analysis of both costs and effects of at least 2 competing strategies and provided an incremental analysis of cost per effect. All treatment strategies for stroke (including ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage) were eligible, including preventive, diagnostic, and therapeutic interventions. We included only those studies with the measure of health effect in quality-adjusted life-years (QALY). Finally, we did not include studies that assessed the primary prevention strategies of antihypertensive treatment or cholesterol management because systematic reviews of these prevention strategies have been performed.16,17

Strategy for Identification of Studies

Relevant cost-effectiveness analyses were identified through searches of the National Library of Medicine’s MEDLINE database, the National Library of Medicine’s HealthSTAR database, Excerpta Medica online (EMBASE), and the Science Citation Index Expanded (SCI-EXPANDED). In addition, a cited reference search was completed for all first authors of identified studies to find additional references. Finally, bibliographies of all relevant articles identified were searched to find additional references (see the Appendix for details of search strategy). Two investigators (R.G.H. and C.G.B.) assessed the title and abstract of each article identified by the above searches to screen for potentially eligible articles. Screened articles were further reviewed to determine whether they met inclusion and exclusion criteria for article eligibility.

Data Extraction

Once articles were chosen on the basis of their inclusion and exclusion criteria, they were reviewed and summary information was extracted. Two abstractors (R.G.H. and C.G.B.) independently reviewed the articles; differences were resolved by discussion. The reviewers were not blinded to study authorship. From each study, we abstracted the following variables: author(s), year of publication, intervention, alternative to the intervention, patient population, perspective of the analysis, study design, health outcome measure, effectiveness data sources, cost data sources, year of costs, time horizon, adjustment for inflation, discount rate, baseline results, variables used in and results of sensitivity analysis, and authors’ conclusions. To aid in this task, we modified the cost-effectiveness analysis reporting checklist published by the Panel on Cost-Effectiveness in Health and Medicine.18

Criteria for Considering an Intervention Cost-Effective

To determine the cost-effectiveness of a particular intervention, we relied on the authors’ conclusions in the primary publication. Most authors considered a cost-effectiveness ratio of less than $50,000 per QALY to be cost-effective. In addition to the ratios reported in the primary publication, we calculate and report here the ratios inflated to 1998 US dollars using the medical component of the consumer price index.

Search Strategy Results

Initial review of the literature yielded approximately 2000 potentially eligible articles. After reviewing their titles and abstracts, the reviewers chose approximately 55 articles to review in detail, 26 of which met study eligibility criteria.19–44

Results

Selected Attributes of Included Studies

Of the 26 included studies (Table 1), 7 focused on pharmaceutical agents,29–33,35,39 7 on surgical procedures,19–21,36,38,42,43 and 12 on radiological procedures.22–28,34,37,40,41,44

Five of the analyses were published in general medical journals,22,25,30,34,39 11 were published in medical specialty journals,6 and 9 were published in surgical specialty journals.30,21,27,28,36,38,41–43 One of the analyses was published in a book chapter.24 Four of the studies received full or partial support from a pharmaceutical sponsor or medical device manufacturer.23,33,35,39

In 25 of the 26 studies, modeling techniques were the principal research method, with Markov modeling used most frequently. In 1 study, the primary research design was a clinical trial that included economic data collection with extrapolation of the clinical and economic consequences by use of modeling techniques.39 In 14 studies (54%), the perspective of the analysis was explicitly stated.24,25,29–37,40,41,43 In 11 of these studies, the perspective was “societal,” whereas in the remaining 3, it was the “healthcare system,”35 third-party payer,31 and “direct medical costs.”39 The time horizon for 23 studies was the remaining lifetime of the patient, whereas in 3 studies, it was 10 years.30–32 Seven of the studies did not show a diagram of the clinical event pathway modeled.19,23,36,38,39,42,44 There was also variability in the scope of costs included in the analyses. For example, all analyses included elements of direct medical costs, but only 4 studies included productivity costs.34,39,43,44 In 9 studies, the methods used to adjust for inflation were not readily apparent.20,23,26,37,38,40–42,44 and in 3 studies, there was no mention of discounting.20,38,41 In 20 analyses, both future effects and costs were discounted to present year values; 6 of the studies used a discount rate of 3% in the base-case analysis.19,23,25,28,34,43 whereas 16 studies used a discount rate of 5%.† In 1 study, 95% confidence intervals were calculated with nonparametric bootstrap techniques;39 otherwise, confidence intervals were not calculated.

Interventions, Alternatives, and Patient Populations

Carotid Endarterectomy

Three studies evaluated the cost-effectiveness of carotid endarterectomy (Table 2).19–21 These studies did not include screening or work-up strategies and began their analyses with an already-defined operable carotid lesion. One article restricted the analysis to asymptomatic patients.29 I restricted the analysis to asymptomatic patients.21 and 1 analyzed both symptomatic and asymptomatic patients.19

Screening and Other Imaging Strategies for Carotid Stenosis

Six studies addressed screening and work-up strategies for carotid artery stenosis.22–27 Five of these studies focused on asymptomatic patients with various underlying prevalence rates of ≥60% stenosis.23–27 Four of these studies addressed the screening policy of carotid duplex ultrasound followed by cerebral angiography, and 1 included the screening policy of

*References 19, 23, 26, 29, 31–33, 35, 37, 40, and 44.
†References 21, 22, 24, 26, 27, 29, 30, 32, 33, 35–37, 39, 40, 42, and 44.
MRA. One study addressed the cost-effectiveness of various perioperative imaging strategies in symptomatic patients, whereas another assessed the cost-effectiveness of postoperative surveillance after carotid endarterectomy by use of duplex ultrasonography to assess progression of carotid artery stenosis.

**Atrial Fibrillation**

Three studies addressed anticoagulation in patients with atrial fibrillation: 2 in patients with chronic NVAF and 1 in patients with mitral stenosis. One study built on a previous study and analyzed a preference-based approach to treatment compared with treating all patients with warfarin.

### Other Ischemic Stroke Interventions

Three other analyses assessed the cost-effectiveness of other ischemic stroke interventions, including rtPA in acute ischemic stroke, ticlopidine in patients with transient ischemic attacks or minor strokes, and TEE and transthoracic echo-
<table>
<thead>
<tr>
<th>Treatment Category/Author</th>
<th>Intervention</th>
<th>Alternative</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid endarterectomy</td>
<td>Carotid endarterectomy</td>
<td>Medical therapy and observation</td>
<td>Asymptomatic and symptomatic 65-year-old men with angiographically confirmed 60%–90% or 70%–99% carotid stenosis</td>
</tr>
<tr>
<td>Kuntz and Kent</td>
<td>Carotid endarterectomy</td>
<td>Medical therapy and observation</td>
<td>Asymptomatic and symptomatic 65-year-old men with angiographically confirmed 60%–90% or 70%–99% carotid stenosis</td>
</tr>
<tr>
<td>Nussbaum et al</td>
<td>Carotid endarterectomy</td>
<td>Medical therapy and observation</td>
<td>Asymptomatic and symptomatic 65-year-old women with prior TIA and presently “well”</td>
</tr>
<tr>
<td>Cronenwett et al</td>
<td>Carotid endarterectomy</td>
<td>Medical therapy and observation</td>
<td>Asymptomatic 67-year-old patients with an operable lesion defined by US</td>
</tr>
</tbody>
</table>

Screen and other imaging strategies for carotid stenosis

| Kent et al                | Perioperative imaging strategies for symptomatic carotid stenosis: MRA, CA, or US | Aspirin | Symptomatic patients, underlying prevalence of operable lesions not specified |
| Derdeyn and Powers        | Screen and CEA when indicated | Aspirin | Asymptomatic 60-year-old men with 4% and 20% prevalence of ≥60% stenosis |
| Matchar et al             | Screen or work-up and CEA when indicated | No screen or work up | 65-Year-old men who are asymptomatic (5% prevalence of operable lesion), asymptomatic with bruit (20%), or symptomatic (50%) |
| Lee et al                 | Screen and CEA when indicated | Aspirin | Asymptomatic 65-year-old men with 5% and 40% prevalence of ≥60% stenosis |
| Obuchowski et al          | Screen and CEA when indicated | No screen | Asymptomatic patients with 10%, 20%, and 30% prevalence of ≥60% stenosis |
| Yin and Carpenter         | Screen and CEA when indicated | No screen | Asymptomatic 60-year-old patients with 5% prevalence of ≥60% stenosis |
| Patel et al               | Postoperative surveillance after endarterectomy with US | No surveillance | Cohort of postoperative symptomatic (>70% stenosis) or asymptomatic (>80% stenosis) patients |

Atrial fibrillation

| Eckman et al              | Warfarin for mitral stenosis and atrial fibrillation | No warfarin | 35-Year-old women with mitral stenosis and atrial fibrillation |
| Gage et al                | Warfarin or aspirin therapy for chronic NVAF | No warfarin or aspirin therapy | 65-Year-old patients with chronic NVAF who are good candidates for warfarin or aspirin |
| Lightowlers and McGuire   | Warfarin anticoagulation in chronic NVAF | No antithrombotic therapy | Patients with NVAF |
| Gage et al                | Preference-based therapy: warfarin or aspirin | Warfarin-for-all therapy | 65-Year-old patients with chronic NVAF who are good candidates for warfarin or aspirin |

Other ischemic stroke interventions

| Oster et al               | Ticlopidine 250 mg BID | Aspirin 650 mg BID | 65-Year-old men and women with recent TIA, RIND, TMB, or minor stroke |
| McNamara et al            | Cardiac imaging strategies (TEE, TTE): treat with anticoagulation those with left atrial thrombus and others with aspirin | Avoid imaging and treat no patients with anticoagulants | 65-Year-old patients in normal sinus rhythm with new-onset stroke and not on anticoagulants or antiplatelet agents |
| Fagan et al               | rtPA within 3 hours of acute ischemic stroke | Placebo | 67-Year-old patients with acute ischemic stroke |

Cerebral aneurysms/subarachnoid hemorrhage

| King et al                | Elective neurosurgical clipping of cerebral aneurysm | Expectant management | 50-Year-old patients with cerebral aneurysm |
| Kallmes et al             | Guglielmi detachable coil embolization for unruptured aneurysms in nonsurgical candidates | No therapy | Neurologically “healthy” patients |
| Gaetani et al             | Early and delayed surgery for subarachnoid hemorrhage caused by ruptured aneurysm | No surgery | 50-Year-old patients with subarachnoid hemorrhage |
Cerebral Aneurysms/Subarachnoid Hemorrhage/Arteriovenous Malformations

One study assessed the clipping of asymptomatic cerebral aneurysms compared with expectant management; another assessed Guglielmi detachable coil embolization for unruptured aneurysms in nonsurgical candidates. One study assessed the cost-effectiveness of early and delayed surgery for subarachnoid hemorrhage caused by a ruptured aneurysm compared with no surgery, and another study addressed the cost-effectiveness of a 10-day course of tirilazad compared with placebo therapy in acute subarachnoid hemorrhage. Two studies addressed the cost-effectiveness of routine angiography (intraoperative and postoperative) compared with no angiography in the management of ruptured aneurysms. Three studies focused on the management of arteriovenous malformations through surgery, stereotactic radiosurgery, or endovascular therapy.

Cost-Effectiveness of Interventions

Carotid Endarterectomy

The cost-effectiveness of carotid endarterectomy for symptomatic carotid stenosis was a dominant strategy in 1 study (Table 3), and was considered an excellent use of healthcare resources ($4100 per QALY) in another study. A third study found carotid endarterectomy cost-effective ($100,000 per QALY) over a great majority of parameters tested except when the efficacy of the endarterectomy fell to 30%, when the durability of benefit was 4.6 years, and when the stroke rate in the nonsurgical group fell <4.6%.

The 2 analyses pertaining to carotid endarterectomy in asymptomatic carotid stenosis yielded cost-effectiveness ratios in the base-case analysis ranging from $8004 per QALY to $52,700 per QALY. These analyses were sensitive to a number of factors, including patient age, annual stroke rate with medical management, perioperative event rate, cost of stroke, and cost of surgery. These analyses did not include a screening strategy to identify appropriate

### Table 3. Cost-Effectiveness of Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Treatment Category/Author</th>
<th>Intervention</th>
<th>Alternative</th>
<th>Year*</th>
<th>Cost/QALY, $</th>
<th>Cost/QALY, 1998 $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nussbaum et al</td>
<td>Aspirin</td>
<td>Not mentioned</td>
<td>CEA dominates†</td>
<td>CEA dominates</td>
<td></td>
</tr>
<tr>
<td>Matchar et al</td>
<td>Aspirin</td>
<td>1994</td>
<td>4100</td>
<td>4715</td>
<td></td>
</tr>
<tr>
<td>Kuntz and Kent</td>
<td>No work-up</td>
<td>1993</td>
<td>38,955</td>
<td>46,746</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cronenwett et al</td>
<td>Aspirin</td>
<td>1996</td>
<td>8004</td>
<td>8484</td>
<td></td>
</tr>
<tr>
<td>Kuntz and Kent</td>
<td>Aspirin</td>
<td>1994</td>
<td>52,700</td>
<td>60,605</td>
<td></td>
</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy.
*Reported year of costs for the analysis.
†CEA is more effective and less costly than alternative.
surgical candidates. This narrowed view systematically biases the results in favor of surgery because it omits the screening costs necessary to identify patients. The studies below include such a screening program.

**Screening and Other Imaging Strategies for Carotid Stenosis**

The 4 analyses that explored the cost-effectiveness of screening and treating patients with asymptomatic carotid stenosis with carotid endarterectomy differed substantially in their cost-effectiveness estimates (Table 4). 

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Alternative</th>
<th>Year*</th>
<th>Cost/QALY, $</th>
<th>Cost/QALY, 1998 $</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-time screening program for asymptomatic carotid stenosis with a 4%–5% prevalence of an operable carotid lesion</td>
<td>No screen</td>
<td>1996</td>
<td>39 495</td>
<td>41 864</td>
</tr>
<tr>
<td>Derdeyn and Powers</td>
<td>Aspirin</td>
<td>1995</td>
<td>52 588</td>
<td>57 847</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Aspirin</td>
<td>1994</td>
<td>120 000</td>
<td>138 000</td>
</tr>
<tr>
<td>Matchar et al</td>
<td>No screen</td>
<td>1993</td>
<td>No screening dominates†</td>
<td>No screening dominates†</td>
</tr>
</tbody>
</table>

Preoperative US and MRA followed by angiography for disparate results in symptomatic patients

| Kent et al | DS alone | 1993 | 22 400 | 26 880 |

Postoperative surveillance with US after endarterectomy

| Patel et al | No surveillance | 1996 | 126 950 | 134 567 |

US indicates Duplex ultrasound.

*Reported year of costs for the analysis.
†The screening program is more costly and less effective than the no-screening program.

Therefore, the authors’ conclusions about cost-effectiveness varied as greatly as the cost-effectiveness ratios. For example, 1 study concludes that “screening for asymptomatic carotid stenosis can be cost-effective when both screening and carotid endarterectomy are performed in centers of excellence.” Other studies conclude that “a program to identify candidates for endarterectomy by screening asymptomatic populations for carotid stenosis costs more per QALY than is usually acceptable” and “strategies involving carotid endarterectomy for asymptomatic patients are difficult to justify.” Interpreting this literature only becomes more confusing when one considers the conclusions of those

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**TABLE 5. Cost-Effectiveness of Anticoagulation in Atrial Fibrillation and Other Ischemic Stroke Interventions**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Alternative</th>
<th>Year*</th>
<th>Cost/QALY, $</th>
<th>Cost/QALY, 1998 $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation for chronic NVAF</td>
<td>Aspirin</td>
<td>1994</td>
<td>Warfarin dominates†</td>
<td>Warfarin dominates†</td>
</tr>
<tr>
<td>Gage et al</td>
<td></td>
<td></td>
<td>$ 8,000</td>
<td>9200</td>
</tr>
<tr>
<td>High-risk patients</td>
<td></td>
<td></td>
<td>$370 000</td>
<td>425 500</td>
</tr>
<tr>
<td>Medium-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightowlers and McGuire</td>
<td>No antithrombotic therapy</td>
<td>1997</td>
<td>Warfarin dominates†</td>
<td>Warfarin dominates†</td>
</tr>
</tbody>
</table>

Anticoagulation for mitral stenosis and atrial fibrillation

| Eckman et al | No anticoagulation | 1991 | 3700 | 5069 |

Other ischemic stroke interventions

| rtPA in acute stroke, Fagan et al | Placebo | 1996 | rtPA dominates† | rtPA dominates† |
| TEE strategies in sinus rhythm stroke, McNamara et al | Image no patients | 1993 | 13 300 | <15 960 |
| Ticlopidine for 5 y, Oster et al | Aspirin for 5 years | 1991 | 39 900 | 54 633 |

*Reported year of costs for the analysis.
†Warfarin/rtPA is more effective and costs less than the alternative.
analyses that did not include a screening program. For example, Cronenwett and colleagues conclude, “Our results indicate that carotid endarterectomy is cost-effective when compared with other commonly accepted health care practices.”

Other evaluations of imaging strategies for carotid disease found preoperative duplex carotid ultrasound followed by MRA (and carotid arteriography for disparate results) in symptomatic patients to be cost-effective ($22,400 per QALY), but postoperative duplex surveillance for restenosis was not ($126,950 per QALY).22,28

Atrial Fibrillation
Anticoagulation with warfarin was dominant to aspirin in high-risk patients (≥2 risk factors) with NVAF. That is, the anticoagulation strategy was more effective and less costly than the aspirin strategy. Anticoagulation with warfarin for NVAF in medium-risk patients (1 risk factor) was considered an excellent investment of healthcare resources ($8000 per QALY), but in low-risk patients (no risk factors), it was considered a poor investment of healthcare resources ($370,000 per QALY).30 Another study confirmed the cost-effectiveness of anticoagulation and extended the findings to those patients >75 years of age (Table 5).31 Anticoagulation for atrial fibrillation caused by mitral stenosis was also considered an excellent investment of healthcare resources ($3700 per QALY).29

Other Ischemic Stroke Interventions
rtPA in acute stroke was found to be a dominant strategy, being more effective and less costly than the placebo alternative.35 Results of cardiac imaging strategies for patients who have had a stroke in normal sinus rhythm strongly suggest that the initial costs of TEE are substantially offset by improved outcome and a reduction in resource use for management of recurrent strokes (Table 5).34 Ticlopidine compared with aspirin was also considered cost-effective, with a ratio of $39,900 per QALY.33

Cerebral Aneurysms/Subarachnoid Hemorrhages/Arteriovenous Malformations
Prompt elective surgery for asymptomatic, unruptured intracranial aneurysms was also found to be a cost-effective strategy ($24,200 per QALY), but this analysis did not include the initial screening costs associated with the surgical strategy, an important omission that, when included, could make surgery less cost-effective (Table 6).36 Endovascular coil embolization of unruptured aneurysms was found to be cost-effective ($19,000 per QALY),37 as was cerebral angiography both during and after surgery for subarachnoid hemorrhage.40,41 Tirilazad mesylate for subarachnoid hemorrhage, the only experimental intervention assessed, had ratios of less than $50,000 per QALY.39 For arteriovenous malformations, 1 study found that embolization and surgery were dominant compared with observation alone.42 Surgery for small, operable AVMs was reported to be cost-effective compared with stereotactic radiosurgery and embolization, with a cost-effectiveness ratio of $7100 per QALY.43

Discussion
Cost-effectiveness research of stroke-related technologies is a dynamic and growing methodological subdiscipline of the general field of medical technology assessment. This field of inquiry addresses 1 dimension of health care: the efficiency with which stroke interventions use medical resources to produce health outputs. This study reveals that many of the stroke evaluation and treatment policies currently available

**TABLE 6. Cost-Effectiveness Interventions for Cerebral Aneurysms, Subarachnoid Hemorrhages, and Arteriovenous Malformations**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Alternative</th>
<th>Year*</th>
<th>Cost/QALY, $</th>
<th>Cost/QALY, 1998 $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral aneurysms</td>
<td>Elective neurosurgical clipping of cerebral aneurysm, King et al</td>
<td>1992</td>
<td>24 200</td>
<td>30 734</td>
</tr>
<tr>
<td></td>
<td>Expectant management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guglielmi coil embolization, Kallmes et al</td>
<td>Not mentioned</td>
<td>19 000</td>
<td>19 000</td>
</tr>
<tr>
<td>SAH</td>
<td>Cerebral angiography during surgery for SAH, Kallmes</td>
<td>No angiography</td>
<td>19 000</td>
<td>20 140</td>
</tr>
<tr>
<td></td>
<td>Cerebral angiography after surgery for SAH, Kallmes</td>
<td>No angiography</td>
<td>22 500</td>
<td>27 000</td>
</tr>
<tr>
<td></td>
<td>Tirilazad mesylate for SAH, Glick</td>
<td>Placebo</td>
<td>1993</td>
<td>50 000</td>
</tr>
<tr>
<td>AVM</td>
<td>Surgery and radiosurgery, Nussbaum et al</td>
<td>Observation</td>
<td>Not mentioned</td>
<td>Surgery dominates†</td>
</tr>
<tr>
<td></td>
<td>Embolization and surgery, Jordan et al</td>
<td>Surgery alone</td>
<td>1992</td>
<td>6734 (Canadian $)</td>
</tr>
<tr>
<td></td>
<td>Surgery for small, operable AVMs, Porter et al</td>
<td>Stereotactic radiosurgery</td>
<td>1995</td>
<td>7100</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage; AVMs, arteriovenous malformation.

*Reported year of costs for the analysis.
†Surgery and radiosurgery is more effective and costs less than observation.
may result in benefits to health that are generally considered worth the cost to produce because they were less than $50,000 to $100,000 per QALY or because they were within the range of other technologies deemed cost-effective. Several interventions may actually save money, in addition to being more effective compared with their alternatives, including anticoagulation for high-risk patients in NVAF and rtPA for acute stroke. In addition, several interventions resulted in health benefits generally not considered worth the cost to produce, including anticoagulation in low-risk patients in NVAF and postoperative surveillance with duplex ultrasonography after endarterectomy.

Previous structured reviews of published economic evaluations have noted only fair adherence to certain fundamental principles. Recent attempts have been made to standardize the conduct and reporting of cost-effectiveness analyses to ensure that those performing such studies are held accountable for their study methods and interpretation. In general, the analyses in our study suggest a greater adherence to the recommended methodological standards than previously reported. However, there is still a room for improvement because only 56% of the analyses stated the perspective of the study, 24% did not provide a diagram of the event pathways, 20% did not state the year of the costs, and 8% did not indicate a discount rate.

By presenting the point estimates of the cost-effectiveness ratios in Tables 3 through 6, one should not assume that there is a high degree of precision around these estimates. Almost all studies performed extensive sensitivity analysis (1 studied calculated 95% confidence intervals). Assumptions about the probabilities used in all analyses (eg, life expectancy, stroke rate, surgical morbidity, and quality of life) are among the most important assumptions made in the analyses. Varying these assumptions 1 at a time while holding all other variables constant is important to assess the stability of the study conclusions and to direct future research by identifying areas of information deficiencies.

When we analyzed the base-case cost-effectiveness ratios from different studies assessing the same intervention, however, the results are more disquieting than reassuring or reassuring. The cost-effectiveness ratios from different studies assessing the same intervention varied by an order of magnitude, leading to widely divergent recommendations. A case in point is the 4 studies that addressed a 1-time screening program for asymptomatic carotid stenosis with a 4% to 5% prevalence of an operable carotid lesion. The interventions and alternatives are very similar, yet 1 study concluded that such a screening program is cost-effective and another concluded that it is detrimental (ie, more costly and less effective). This lack of agreement among the studies addressing the same intervention reduces confidence that these analyses are reliably measuring the outcome (ie, cost-effectiveness) they purport to measure. This also raises concerns about the validity of the other studies, particularly given the discretionary nature of these models and the potential biases that can enter into such evaluations.

Differences in model structure and input variables may partially explain these divergent conclusions. Understanding and reducing this source of variation are critical if the results from these analyses are to be used by clinicians and health policy makers. To date, no information is available as to how these stroke-related analyses have influenced clinical practice or health policy, including formulary or coverage decisions within managed care or the government or in changing how stroke care is organized and financed. In fact, there is little indication that cost-effectiveness analyses have contributed more broadly to resource allocation or reorganization decisions within the United States.

Given the results of this study, one wonders whether the results of these analyses should be relegated to a limited role in shaping policy and in guideline development, at least for the present time. It is hoped that data emerging from the Stroke Prevention Policy Model, a comprehensive model of stroke development and outcome, will further extend these observations and provide clinical and policy answers to questions concerning stroke prevention.

A corollary to the problem above is ensuring that the analysis addresses the right research question. Three of analyses in this study that assessed the cost-effectiveness of a surgical intervention (carotid endarterectomy in asymptomatic patients, surgical clipping of an aneurysm) should have arguably included the screening costs and effects associated with identifying the patient populations. Because the cost of screening patients for carotid disease or aneurysms is high and accrued in only 1 of the treatment arms, its omission will tend to underestimate the total costs of the surgical strategy and make the cost-effectiveness ratios for surgery appear more favorable. Thus, critical appraisal and judicious interpretation of cost-effectiveness research are essential.

To be most useful, these analyses should also be systematically updated as new research emerges. For example, new data from the International Study of Unruptured Intracranial Aneurysms (ISUIA) would better inform the analysis performed by King and colleagues. In the ISUIA study, the yearly aneurysm rupture rate was found to be much lower than previously thought (0.05%) and 20 times lower than the rate used in the base case of the model (1%), a change that would make surgery less cost-effective.

Despite the limitations noted in this study, cost-effectiveness research has provided new insights into the economics of stroke and the value of stroke prevention and treatment. The economic toll of stroke is of increasing importance as healthcare systems seek to contain costs while maintaining—or improving—quality of care. Because stroke is enormously disabling and expensive, it is likely that even modestly effective therapies are likely to be of good value. The burden of proof, however, depends on the careful conduct of cost-effectiveness analyses of stroke-related technologies and critical appraisal of the results. Only then can the medical community translate the knowledge gained from these studies into strategies for promoting improvements in the prevention and treatment of stroke.

Appendix

The National Library of Medicine’s MEDLINE database (SilverPlatter 3.11; 1966 through January 1999) was systematically searched with the use of the following strategy:

1. Explode cerebrovascular disorders—all subheadings (set 1).
2. Explode costs and cost analysis—all subheadings (set 2).
3. Explore technology assessment, biomedical—all subheadings (set 3).
4. Combine sets 1 through 3 (set 4).
5. Limit set 4 to the English language (set 5).

HealthSTAR (1975 through January 1999) was systematically searched with the strategy detailed above for MEDLINE and limiting to non-MEDLINE records.

EMBASE (1980 through January 1999) was searched with the use of the following general strategy.

1. Explore economic aspect (set 1).
   - “0139”.tg. to represent a compilation of economically associated terms into a single entry.
2. 1 or 2 (set 3).
3. Explore cerebrovascular disease—all subheadings (set 4).
4. 3 and 4 (set 5).

The Science Citation Index Expanded (SCI-EXPANDED; 1988 through March 1998) was systematically searched with the use of the following sets of terms in a general search. The “*” indicates truncation of terms.

Stroke* and cost*.
Stroke* and cost-benefit analys*.
Stroke* and cost-benefit analys*.
Stroke* and cost-effective*.
Stroke* and econom* evaluat*.

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Robert G. Holloway, Curtis G. Benesch, Catherine R. Rahilly and Caryn E. Courtright

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